REMARKS

Claims 1 and 5 have been amended. Claim 4 has been canceled without prejudice. New claim 15 has been introduced into the application. Submitted herewith is a substitute specification along with copies of the originally filed papers but for the specification.

The present invention is in a pharmaceutical formulation. Prior to the present invention, the preferred method of production of microcapsules was by spray drying from a solution. However that method would not produce a coated powder having sustained release properties. While not wishing to be bound by theory the traditional teaching is that sustained release properties could not be obtained because the coating was too porous. The speculation was that the porous coating resulted because of the formation of blow holes in the final coating. Such blow holes were not necessarily deleterious to the taste masking properties of the coating since the rate of diffusion of active compound through these blow holes was not rapid enough to be noticeable given the short residence time in the mouth during administration. However, such a porous coating compromises the sustained release properties. Therefore, the conventional wisdom was that a spray drying process would not produce a particle having both adequate taste masking and sustained release properties. See the previously submitted Deasy article.

In contrast to that teaching, Applicants have overcome these problems as evidenced by the bioavailability study shown in Table 2 which demonstrates that the powders of the present invention provide sustained release properties when compared to non-coated products. Accordingly the applicants present invention provides a significant improvement over the prior art.

Claims 1, 6, 8, 11 and 13 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,767,789 to Blank (Blank). It is submitted this rejection is improper and should be withdrawn.

For a single reference to anticipate a claimed invention, that reference must show each and every feature of the claimed invention and those features must be arranged as in the claimed invention. Thus, Blank is not an anticipatory reference as a matter of law and the rejection under 35 U.S.C. § 102 is in error as a matter of law. See Connell v. Sears Roebuck & Co., 220 U.S.P.Q. 193 (Fed. Cir. 1983).

Blank is directed to an immediate release taste masked spray dried product. Blank states:

> "This invention relates to a novel therapeutic form of spray dried acetaminophen having a neutral taste which can be formulated into for example, fast dissolving dosage forms as described in U.S. Pat. Nos. 4,3O5,5O2 and 4,371,516.
>
> See col. 1, lines 6-11.

Those latter references describe " the fast dissolving dosage forms" which "disintegrate in water within five seconds or less and hence dissolve rapidly in the saliva of the mouth".

Thus, assuming Blank's spray dried powders has taste masking properties, there is no teaching or suggestion that Blank's product exhibits sustained release properties. Indeed, Blank's products are immediate release type products. In contrast, the present invention is in a spray dried product which is both sustained release and taste masking.

There is no suggestion in Blank that sustained release properties can be obtained using the spray drying techniques described therein. As discussed above, one skilled in the art on reading Blank in light of the teaching of the Deasy review would not consider Blank to disclose a sustained release formulation nor is there any teaching or suggestion that this is achieved. As discussed previously, while taste masking is an important objective possibly addressed by Blank, the present invention also provides the additional important feature in that the powders thus produced have sustained release properties as evidenced by the data set forth in the examples of the present application.

The Examiner states that Blank refers to his coating as "about 24% to 40% by weight". However, this must be read in the context of the entire disclosure. At column 2, lines 3 to 9, Blank states that the weight percent of the ethylcellulose can range from 24% to 40% by weight." Accordingly, there is no disclosure in the body of the specification supporting lower amounts of ethylcellulose than 24% in Blank. As such, it is respectfully submitted that Blank is not enabling for amounts of ethylcellulose below 24% by weight.

In addition, Applicants respectfully disagree with the Examiner's contention that the phrase "about 24%" encompasses a difference of a few percentage points. At best, it is that phrase encompasses amounts within measurement error of this figure. All examples of Blank show measurement of the ethylcellulose weight percentage to two decimal places. Accordingly, even if the figure for ethylcellulose is variable, Applicants respectfully submit that it does not vary by up to 1% and accordingly the pending claims are novel over Blank.

Further, attention is invited to column 1 wherein the patentee describes his invention as relating to a "taste neutral spray dried powder". If that is the understanding one of ordinary skill in art would have of Blank, in this context, then he would also seriously consider

column 2 at about line 6 wherein the patentee indicates that "At 25% by weight of ethylcellulose, there is a slightly bitter taste but at 26% and above the powder is taste neutral". Clearly, to obtain the objective of the invention, i.e. "taste neutral" as recited in column 1, one would understand he must use above 25% otherwise there is a bitter taste. Blank continues at lines 8 and 9 that at 26% and above the powder is taste neutral. Therefore, one of ordinary skill in the art would not, based on Blank, consider using less than 25% and certainly no less than 24% to achieve the "taste neutral" objective. Certainly they would not consider Blank's "about" phraseology to include a range giving a bitter taste. Thus, Blank does not anticipate the now claimed subject matter.

In view of these teachings by Blank and the amendment to claim 1, the Examiner's statement of burden shifting is no longer pertinent. However, it is believed that the Examiner's assertion is incorrect but since that issue now appears to be moot, Applicants will not address the issue further.

Claims 1, 6, 9 and 13 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,707,646 to Yajima et al. (Yajima). It is submitted the rejection is improper and should be withdrawn.

It is noted that the rejection does not address the specific limitations of the claims. Nothing in the Office Action discussing the Yajima reference or in the reference itself indicates that a substantially continuous polymer coating is formed and that the resulting product has sustained release properties or that the coating comprises less than 23% by weight of the formulation. Thus, Yajima, as a matter of law, cannot anticipate the now claimed subject matter.

Yajima relates to a taste masked pharmaceutical formulation comprising clarithromycin. However, Applicants take issue with the Examiner's characterization that the production is produced by spray drying a mixture. The spray drying process as described in

the present application as understood by one skilled in the art involves the dispersion of the active constituents and the polymeric coating in a solvent followed by evaporation of the solvent through the use of a spray dryer. Generally the solubility of the drug to be used in the solvent is lower than the solubility of the coating agent in the solvent. Accordingly, as the solvent particles evaporate the active agents crystallize and a liquid coating, which comprises the solvent and the still dissolved coating polymer, form about them. With continued solvent evaporation the coating polymer is no longer soluble in the remaining solvent and crystallizes forming a continuous polymer coating around the active drug (which acts as a seed crystal for the polymer). This leads to the improved coating properties of the present invention as it affords almost a discrete core of active constituent surrounded by a discrete polymer coating. Furthermore, in some cases of spray drying the solvent is chosen so as not to dissolve the active ingredient at all i.e. the active ingredient stays crystalline throughout the process, and during the spray drying process the polymeric coating dries around the already crystalline active ingredient.

In contrast, Yajima's process, illustrated in patent Example 1, while using a spray dryer apparatus does not conduct a conventional spray drying process. In actuality, Yajima describes the use of the spray dryer as a means of conducting a spray cooling operation to form a granulate. Thus, no solvent is used and the examples merely describe the situation where two polymers are heated above their melting point and clarithromycin is then dispersed therein. Following this dispersion the material is pumped through the apparatus to atomize it into small particles which on cooling solidify to form granules. Thus, Yajima uses the apparatus for heat transfer only, not for mass transfer or a combined heat/mass transfer operation.

In Yajima, there is no spray drying *per se* occurring and therefore there is no assurance in this method that a continuous polymer coating on the active ingredients will be achieved. Indeed, there is an equal probability that the active particles would be on the surface of the granulate as opposed to the present invention which leads to all active particles having a polymeric coating therein. Accordingly, it is submitted that Yajima does not disclose the subject matter of the now claimed invention. There is simply no teaching of, *inter alia,* the spray drying or the coating weight of the formulation.

Claim 1 to 8, 11, 13 and 14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Blank. It is submitted the rejection is improper and should be withdrawn.

As set forth above, Blank contains a teaching that the ethylcellulose must be present in the ranges from 24 % to 40 % by weight (see column 2). Furthermore. at line 6 of this column it is noted that Blank states "at 25 % by weight of ethylcellulose, there is a slightly bitter taste but at 26 % and above the powder is taste neutral." Accordingly, a skilled artisan on reading Blank which teaches that levels of the coating of less than 24 % by weight are undesirable would not be motivated to modify Blank or understand him to suggest coating weights of less than 24%. Thus, there is no motivation for one of ordinary skill in the art to modify the disclosure of Blank. It is submitted that Blank teaches away from the now claimed invention. Accordingly, it is respectfully submitted that the proposed amended claims are patentable over Blank.

Applicants further take issue with the Examiner's statements regarding the use of a two fluid nozzle spray dryer. The Examiner has attempted to characterize this claim limitation as optimization. However, this is error.

The recited subject matter is a limitation of the claim and must be considered irrespective of whether it is critical to the invention or not. The Examiner cannot merely characterize a feature of an invention as optimization without citing art to this effect. Further, the Examiner's statement of motivation is not understood in the context of a rejection based on a single reference. If the Examiner is suggesting modifying the disclosure of Blank and motivation for such a modification, this is improper. The Examiner's attention is invited to *In re Hummer*, 113 U.S.P.Q. 66, 69 (CCPA 1957) wherein it was held that a prior patent is a reference only for what is clearly discloses or suggests and that it is an improper use of a patent as a reference to modify its structure to one which it does not suggest. The Examiner has not, on the record, cited to anything in the reference to suggest the modification. Accordingly, the rejection for obviousness is improper and should be withdrawn.

Claims 1 to 9, 11, 13 and 14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Blank in view of Yajima. It is submitted this rejection is improper and should be withdrawn.

As discussed above it is respectfully submitted that Blank teaches away from the now claimed subject matter. Accordingly, for the above stated reasons, it is submitted that one of ordinary skill in the art would not be motivated to combine the teachings of Blank with the teachings of Yajima. Based on Blank, one of ordinary skill would expect that using a coating weight of less than 24% (indeed using a coating of less than 26%) would not give effective taste masking. Thus, there is no motivation to combine the teachings of Blank and Yajima or to utilize ethylcellulose levels of less than 26 %. Furthermore, one would not be motivated to combine a reference that relates to spray drying with one that relates to spray cooling The dynamics of these two processes are different as are the expected resultant products.

Accordingly, this combination of references, even if proper, would not suggest the now claimed invention.

Claims 1 to 9, 11, 13 and 14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Blank in view of U.S. Patent No. 4,808,411 to Lu. It is submitted this rejection is improper and should be withdrawn.

The comments set forth above as to the Blank reference should be considered as repeated herein at length.

The Lu reference discloses a complex of carbomer (acrylic acid polymers) and erythromycin or a derivative thereof. Lu's compositions are prepared by dispersing the drug, such as erythromycin, in a suitable organic solvent such as ethanol or acetone, and dispersing the carbomer separately in ethanol, mixing the two solutions slowly to allow formation of the reaction product and then evaporating most of the solvent and diluting the solution with water. The reaction product is recovered by filtration and is then dried. This reference gives no indication of the weight percent of the coating. The Examiner apparently cites Lu for its disclosure of particle size range. However, none of the particle size ranges disclosed in Lu correspond with, or suggest, those set forth in claims 2, 3 or 7. Thus, it is not understood why the Examiner has cited this reference in view of her comments on Lu in the Office Action. Further, there is no motivation is either Blank or Lu to combine these two references and even if the combination of references were proper, they would not suggest the now claimed subject matter. It is further submitted that the disclosure of "less than 270 μ" does not suggest the specific ranges now claimed.

Claims 1 to 9, 11, 13 and 14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Blank in view of U.S. Patent No. 5,378,474 to Morella (Morella). It is submitted the rejection is improper and should be withdrawn.

As before, the foregoing comments with respect to the Blank reference should be incorporated in the response to this rejection as if set forth herein at length.

A spray drying process as described in Blank typically begins with a mixture of solid active compound, a solvent, and a coating material which is soluble in the solvent. Additional additives can be used which are either soluble or insoluble in the solvent in the spray drying process. The material is then transported to the spray dryer in which evaporation of the solvent occurs. This leads to an increase in concentration of the dissolved components in the solvent resulting in their coming out of solution and coating the insoluble particles. Accordingly, when the spray drying process is used it is typical that the insoluble components will end up being coated by the dissolved components. The insoluble components therefore will normally end up in the core of the produced material.

One of ordinary skill in the art would not be motivated to combine the teachings of Morella with the teachings of Blank. Blank is directed to a spray drying process whereas the Morella coating process is not spray drying but instead is a fluid bed coating process. See col. 15, lines 40-50 which state that Morella is directed to the production of pellets. One of ordinary skill in the art would understand that fluid bed processes and spray dryer processes are significantly different coating processes leading to significantly different products being produced and that the teachings from one process of making coated particles can not necessarily be carried over into a teaching of another production technique. Morella relates to a sustained release pharmaceutical composition of three components as follows:

1. at least one polymer which is substantially insoluble independent of pH (insoluble matrix polymer);
2. at least one enteric polymer which is substantially insoluble at acidic pH but at least partially soluble at a less acid to basic pH (enteric polymer): and
3. at least one component which is at least partially soluble at acidic pH (acid soluble polymer).

Morella provides a positive teaching starting at col. 8, line 46 that "[I]t has been found necessary in order to achieve a slow rate of release at acidic pH for pH dependent or independent drugs, and faster relatively constant rate of release over an extended period of time to include the above three components in the hybrid core coating composition."

One of ordinary skill in the art would therefore understand from the teachings of Morella that in order to achieve sustained release that these three components are necessary, not merely optional. The skilled art worker would understand however that the coatings referred to by Morella include solid components (as one of the components is insoluble). One of ordinary skill would therefore understand that if such a component were used in a spray drying approach as described in Blank the solid components would end up in the core of the particle and not in the coating. The result promised by Morella would therefore not be achieved. One of ordinary skill would understand that the teachings in Morella are limited to batch granulation or fluid bed type processes in which the solid core is preformed and is then coated. A process such as a spray drying process wherein the solid core is not preformed would not be amenable to modification by the teachings of Morella. Accordingly, Applicants must respectfully disagree with the Examiner's position that one of ordinary skill would be motivated to coat the formulation of Blank according to the coating amount and thickness from

Morella with a reasonable expectation of obtaining a pharmaceutical composition that has good taste masking properties and provides sustained release.

As previously indicated, there is no motivation for one of ordinary skill in the art to choose the parameters as has been chosen by the Examiner from the Morella reference such as "the amount of coating, the size of the core, and the thickness of the coating" for use in the method of Blank with a reasonable expectation of achieving a taste mask pharmaceutical preparation with controlled release.

Firstly, Blank discloses a concrete teaching as referred to previously that at a coating of less than 24 % effective taste masking cannot be achieved. Furthermore, one skilled in the art on reading Morella would know that the properties in relation to taste masking are achieved by a number of factors including the nature of the coating and the way in which it is applied The parameters that the Examiner appears to have cherry picked from Morella in an attempt to combine it with Blank would not necessarily be seen by a skilled artisan as the important factors.

Morella uses three polymers in the coat and contains a plasticizer and talc. Morella describes making these much larger particles via a fluid bed coating process instead of spray drying. There would simply be no reason for a person skilled in the art to consider combining the references. One of ordinary skill would understand Morella as suggesting that the beneficial properties described therein result from the particular combination of coating materials and the method of coating and not from the amount of coating, the size of the core or the thickness of the coatings. In particular, one of ordinary skill on reading both Blank and Morella would be further encouraged in this belief. On the basis of Blank one would consider that it was necessary to have at least 24 % and preferably at least 26% of the coating in order

to achieve adequate levels of taste masking. If, as alleged by the Examiner, the Morella reference provides a teaching that this can be avoided (which the Applicants deny) the Applicants submit that it would not be seen as due to being the parameters referred to by the Examiner. A more likely explanation is that the skilled artisan would consider that the multi component coating mixture of Morella and, the milder conditions employed in the fluid bed process, lead to the improved properties. Accordingly, the Applicants submit that should one be tempted to modify the teachings of Blank using the teachings of Morella at best they would be lead to using the multi component mixture of Morella in a fluid bed process to achieve this coated particle. In particular, as noted in the earlier response, one of ordinary skill would know that the teachings of Morella could not be used in the process of Blank as the teachings of Morella (which includes talc coating) would not be conducive to spray drying. Furthermore, a person skilled in the art would understand a pellet as having an average particle size of a much larger size than that of a powdered composition. As such, it is respectfully submitted that the amended claims are inventive over this combination.

In Paragraph No. 18 the Examiner states that "U.S. '474 is relied upon merely to show that it is known to one in the art to use the particle sizes and percentages of coating in this claim". Applicants submit that this is an improper use of the Morella disclosure. Morella must be read in context and should not be used to support the generalized proposition that the Examiner appears to consider important that coating level, size of the core and coating layer as described in Morella can be used to achieve taste masking. This proposition is simply not correct as it must be read in the context of the disclosure of Morella which limits the proposition to be correct when the particular coating method and coating composition as used in Morella are utilized. It is therefore submitted that the Examiner has erred in extending the

teachings of Morella far beyond what is actually disclosed and one of ordinary skill, on reading Morella and Blank, would not be motivated to arrive at the present invention.

It is further submitted that the combinations of references are improper. As discussed above, each of the references list different techniques to obtain different products with different characteristics. It is clear that the Examiner has engaged in a pick and choose technique based on hindsight using Applicants' invention as a blueprint to selectively edit the cited references. This is improper. See In re Grabiak, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Further, the manner in which the Examiner has edited the references for the combination would require that salient features of the respective disclosures of the references and important features of the invention as disclosed therein be ignored. This is also improper for a rejection under 35 U.S.C. § 103. See In re Ratti, 123 U.S.P.Q. 349 (CCPA 1959).

Applicants have noted the Examiner's response to arguments but in some instances are very confused by the Examiner's comments. In Paragraph No. 12, the Examiner says that none of the claims require sustained release or taste masking. However, claim 1 and new claim 15 recite that the continuous polymer coating achieved taste masking and sustained release of the compound.

Further, the Examiner's assumption that one would reasonably expect that spray drying could produce a sustained release product and also provide taste masking is not, as is required, supported by art of record.

The Examiner has cited *In re McLaughlin* to justify the combination of references. However, the Examiner's explanation prior to the citation of *In re McLaughlin* is erroneous. First it is noted that *In re McLaughlin* was decided long before the creation of the Federal Circuit Court of Appeals. Secondly, Applicants have cited the proper standard in the

prior Amendment and repeated that in this Amendment. In this regard, the Examiner's attention is invited to *In re Grabiak, supra.*

In view of the foregoing, reconsideration and allowance of the application with claims 1 to 15 are earnestly solicited.

The Examiner is invited after reviewing the foregoing to phone Applicants' undersigned attorney to advise of the status of the matter or to resolve any remaining issues.

Respectfully submitted,

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Enclosures: Transmittal letter submitted to USPTO 10/28/98
General Authorization For Payment of Fees submitted to USPTO 10/28/98
Filing Fee Computation Sheet submitted to USPTO 10/28/98
Substitute Specification (identical to that submitted to USPTO 10/28/98)
Three sheets of drawings submitted to USPTO 10/28/98
Preliminary Amendment submitted to USPTO 10/28/98